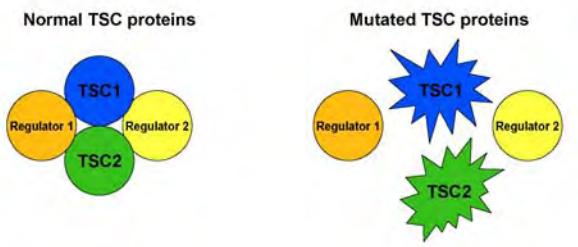
# Congressionally Directed Medical Research Programs
# Tuberous Sclerosis Complex Research Program

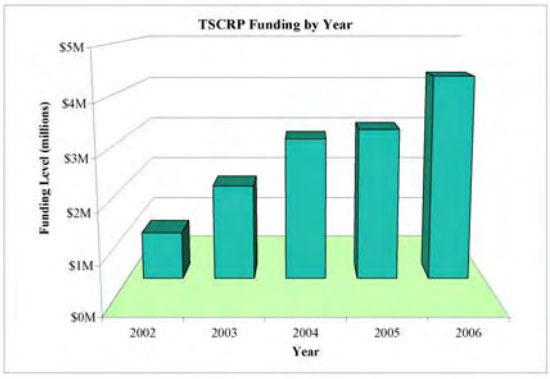
## Introduction to Tuberous Sclerosis Complex (TSC)

TSC is a genetic disorder that affects as many as 50,000 individuals in the United States and about 1 to 2 million individuals worldwide. TSC causes tumors in many different organs, especially in the brain, eyes, heart, kidney, skin, and lungs. TSC is also characterized by seizures, developmental delays, behavioral problems, autism, and mental retardation. Major research breakthroughs have identified two genes, TSC1 and TSC2, whose dysfunction causes TSC. The TSC1 gene is located on chromosome 9 and produces a protein called TSC1 (hamartin). The TSC2 gene is located on chromosome 16 and produces a protein called TSC2 (tuberin). These proteins normally interact with each other and with important cell regulatory proteins; mutations in TSC1 or TSC2 disrupt these communications. The discovery of the TSC1 and TSC2 genes is a giant step forward in the fight against TSC, as they provide excellent targets for the development of new diagnostic assays and therapies for TSC.




## Overview of the Tuberous Sclerosis Complex Research Program (TSCRP)

Grassroots efforts by the TSC advocacy community led to congressional appropriations to the Department of Defense (DOD) of $1 million (M) in Fiscal Year 2002 (FY02) for TSC research. Since then, a total of $13.5M has been appropriated, including $4.3M for FY06. This funding energized the development of a unique partnership among the public, Congress, and the military. The Congressionally Directed Medical Research Programs (CDMRP) within the U.S. Army Medical Research and Materiel Command (USAMRMC) manages the TSCRP. The TSCRP is conducted according to the two-tier review model recommended by the National Academy of Sciences Institute of Medicine; this model has received high praise from the scientific community, advocacy groups, and Congress. Today, the TSCRP is one of the leading sources of extramural TSC research funding in the United States.




The TSCRP fills important gaps in TSC research not addressed by other funding agencies. The TSCRP vision is adapted yearly to facilitate rapid change and to better target funding to the most critical TSC research areas, thus ensuring that the program remains responsive to current needs and future opportunities.

## Vision of the TSCRP

The vision of the TSCRP is to lessen the impact of TSC. To accomplish this, the TSCRP supports innovative research, including natural history studies, aimed at understanding the role and function of proteins produced by the TSC1 and TSC2 tumor suppressor genes and improving diagnosis and treatment of TSC. The TSCRP is particularly interested in finding and funding innovative, high-impact research that seeks to (1) detect and diagnose TSC and (2) treat TSC.

# Unique Features of the TSCRP

## Consumer Advocate Participation


A unique feature of the TSCRP is that consumer advocates actively participate in setting program priorities and making funding decisions. Consumer advocates may be individuals with TSC or have family members with TSC (TSC initially manifests in childhood). Their firsthand experience with TSC provides a unique perspective that helps the scientists understand the human side of the disease and allows for funding decisions that reflect the concerns and needs of patients, their families, and clinicians. Consumer advocates also share what they have learned with their communities, resulting in increased awareness of the importance of research and a stronger relationship between the scientific community and the consumer advocate community. The overwhelming success of the inclusion of consumer advocates in the review process for CDMRP programs such as the TSCRP has influenced other funding agencies to follow this precedent.

*"I feel privileged to be involved as a consumer reviewer for the CDMRP. The efficiency, the professionalism, the commitment, the constant conscious and conscientious effort to ensure that not one penny of our precious resources goes to waste are outstanding and must be commended."*
Patrick Sheffield, TSCRP Consumer Peer Review Panel Member

## Program Focuses

In order to fill important research gaps, the TSCRP has focused on two broad areas:

- Exploring Innovative, Groundbreaking Ideas and Technology: supporting high-risk and high-reward research of exciting new ideas
- Impacting Patients' Lives: bringing new discoveries to patients through clinical research

# Research Funding Strategy of the TSCRP

The TSCRP has implemented research award mechanisms that are specifically aimed at minimizing the impact of TSC.

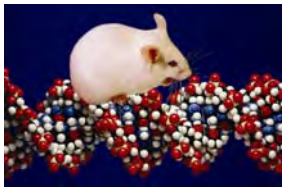
| Exploring Innovative, Groundbreaking Ideas and Technology | Impacting Patients' Lives |
|---|---|
| **Idea Development Award:** Supports innovative research directed toward improving detection, diagnosis, and treatment of TSC | **Natural History Award:** Funds focused, hypothesis-driven natural history studies to enhance the current knowledge of TSC manifestations and improve clinical management |
| **Concept Award:** Funds high-risk, high-reward research toward the exploration of novel theories or development of new preclinical tools | **Clinical Resource Development Award:** Supports the development and testing of breakthrough technologies for measuring TSC-relevant clinical or surrogate endpoints in clinical trials |

# Success Stories

## Exploring Innovative, Groundbreaking Ideas and Technology

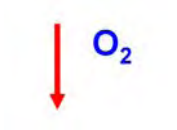
### Idea Development Awards

*Discovering the functions of TSC1 and TSC2*. Dr. Elizabeth Henske of Fox Chase Cancer Center is using yeast model systems to learn new functions of the TSC1 and TSC2 proteins. Understanding the functions of TSC1 and TSC2 will speed the development of new targeted therapeutics. Dr. Henske's research team showed that deficiencies in TSC1 and TSC2 caused abnormal amino acid sensing, uptake, and metabolism. Diminished uptake of the amino acid glutamate is believed to contribute to seizure development, suggesting that the yeast model may provide a novel system for the study of TSC-related epilepsy and for preclinical screening of new therapeutics that may reduce seizures.

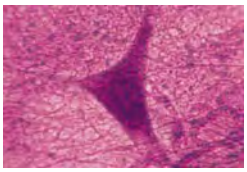


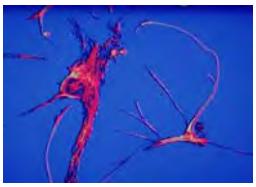
*Understanding the causes of TSC-related epilepsy.* Dr. David Gutmann of Washington University School of Medicine discovered new mechanisms by which TSC gene defects in the brain result in seizures. Dr. Gutmann and colleagues used mouse models to study molecular and cellular effects of decreased TSC1 in the brain. The researchers discovered several genetic and cellular abnormalities that result from astrocyte-specific inactivation of TSC1, showed a role for astrocyte potassium homeostasis in influencing seizures, and developed a novel concept that the astrocyte may be centrally involved in the pathogenesis of neurological complications of TSC, including epilepsy. These findings suggest that astrocytes could provide targets for new innovative therapies against epilepsy.

*Discovering how TSC2 mediates cell growth in response to oxygen deprivation*. Dr. William Kaelin of the Dana-Farber Cancer Institute studied how TSC2 mediates signaling pathways in response to hypoxia, or oxygen deprivation. Tumor hypoxia is associated with a negative prognosis in several types of cancers, including those associated with TSC. Dr. Kaelin's research team dissected signaling pathways involving TSC2 and mTOR, a central regulator of protein synthesis and cell growth found at high levels in TSC patients. They discovered that inhibition of mTOR in hypoxic cells requires a functional TSC1/TSC2 protein complex. Moreover, inactivation of TSC2 conferred a proliferative advantage to cells grown under hypoxic conditions. Improved understanding of the role of TSC2 in response to hypoxia could lead to better treatments for tumors associated with TSC.




*Determining how TSC1 and TSC2 contribute to neurological disorders.* Dr. Bernardo Sabatini of Harvard Medical School is uncovering mechanisms that underlie neurological disorders in TSC. His research team tested his hypothesis that the function of each neuron is perturbed in patients with TSC and that, because of these defects in each brain cell, the brain as a whole does not function properly. In contrast, a conventional hypothesis is that the presence of tumors within the brain creates a disorganized brain architecture. Dr. Sabatini's team manipulated TSC1 and TSC2 levels in animal and cell models and then examined single cells. They found that the TSC pathway regulated cell size, the density and size of dendritic spines (cell extensions that are information transfer sites), and the properties of excitatory synapses (spaces where signals transfer between nerve cells) in neurons. These results indicate that the TSC pathway regulates neuronal structure and function, and disruptions of this function in individual cells contribute to neurological symptoms of TSC.





*Discovering how TSC proteins regulate cell movement.* Dr. Vera Krymskaya of the University of Pennsylvania uncovered mechanisms by which TSC1 and TSC2 regulate cell adhesion and motility. Cell motility is particularly important in the correct positioning of neurons during brain development. Abnormal cell motility also leads to lung tumors, or lymphangioleiomyomatosis (LAM), in TSC patients. Dr. Krymskaya and colleagues found that TSC2 modulates actin dynamics and cell adhesion and plays a critical role in modulating migration and invasiveness of LAM-derived cells. They also discovered that TSC1 and TSC2 regulate Rho and Rac, two proteins that are key regulators of cell shape and motility. Rho and Rac also play critical roles in tumor invasion and metastasis. These findings are important in developing new therapeutic strategies to treat neurological disorders and lung tumors in TSC patients.

## Impacting Patients' Lives

### Natural History Studies

*Natural History Development Award: Developing a comprehensive clinical database.* Dr. Steven P. Sparagana of Texas Scottish Rite Hospital for Children and the University of Texas Southwestern Medical Center at Dallas, in collaboration with the Tuberous Sclerosis Alliance and other clinicians caring for patients with TSC, is developing a comprehensive clinical database of TSC that documents the natural history and variability of TSC over the lifespan of individuals with the disease. Understanding the clinical aspects of TSC could yield more accurate prognosis of disease course, help identify and develop targeted treatments, and help predict patient response to treatments.

*Natural History Study Award: Determining the natural history of kidney angiomyolipomata.* Dr. John Bissler of the University of Cincinnati is concentrating on the natural history of renal (kidney) complications from TSC. His research team is using imaging to study angiomyolipomata (abnormal growths consisting of blood vessels, muscle cells, and fat cells) found in 80% of TSC patients. These lesions can cause severe pain and renal failure. Understanding the natural history of these lesions and understanding which lesions are most likely to grow quickly or develop aneurysms will greatly assist clinical care of patients with TSC.

## Summary of TSCRP Research Highlights

Impacting TSC-associated neurological diseases.

- Discovery of mechanisms underlying epilepsy (Dr. Elizabeth Henske and Dr. David Gutmann)
- Discovery of how TSC1 and TSC2 alter the structure and function of single neurons (Dr. Bernardo Sabatini)
- Identifying how TSC1 and TSC2 regulate brain development (Dr. Vera Krymskaya)
- Determining the natural history of epilepsy, cognitive development, and behavioral disorders (Dr. Steven Sparagana)

Impacting TSC-associated tumors and kidney diseases.

- Discovery of mechanisms of TSC2-mediated responses to hypoxia (Dr. William Kaelin)
- Identifying how TSC1 and TSC2 regulate metastasis of lung tumors (Dr. Vera Krymskaya)
- Determining the natural history of kidney angiomyolipomata (Dr. John Bissler)

http://cdmrp.army.mil/tscrp

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